PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REG/G20580WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/001583	International filing date *(day/month/year)* 22.04.2004	Priority date *(day/month/year)* 24.04.2003

International Patent Classification (IPC) or national classification and IPC
C12N15/12, C07K14/47, A61K38/17, A61K39/35, G01N33/567

Applicant
CLINOVATION et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.2005	11.04.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/001583

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-18	as originally filed

Sequence listings part of the description, Pages

1-5	as originally filed

Claims, Numbers

10-21	as originally filed
1-9	received on 14.01.2005 with letter of 13.01.2005

Drawings, Sheets

1/9-9/9	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/001583

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18, 20 and 21
	No:	Claims	19 (No Assessment, see section V, item 6.2)

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

SECTION I

1. Amended **claims 1- 9** filed with your letter of 13.01.05 are considered to be allowable under **Rule 70.2 (c) PCT**.

SECTION II

2. The International Preliminary Examination Report has been established considering that the **priority date** 24.04.03 is validly claimed. Therefore, document J. Biol. Chem., Vol. 278, no. 41, 10 October 2003, pages 40144-40151, has not been considered to be part of the prior art as defined in the regulations (**Rule 64 (1) and (3) PCT**).

SECTION V

3. Reference is made to the following documents:

   D1: WO 00/20032
   D2: J. of Allergy and Clinical Immunology, Vol. 110, no. 5, 2002, pages 757-762

4. Novelty (**Article 33(2) PCT**)

   The subject-matter of the present application does not appear to be disclosed in the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).
   Therefore, in view of such prior art the subject-matter of the present application (**claims 1-21**) has to be regarded as being new (**Article 33(2) PCT**).

5. Inventive Step (**Article 33 (3) PCT**)

   The **closest prior art** to evaluate the inventiveness of the present application is any of documents **D1 or D2**.
   Both documents **D1 and D2** disclose the recombinant cat allergen Fel d 1 as a fusion product, in which the two chains, chain 1 and chain 2, are expressed in series and linked together by a 19 amino acids linker which comprises restriction sites on both sides of the linker.

The difference between the D1/D2 and the claimed subject-matter if that the linker used in the present application is shorter.

Starting from **D1 or D2**, the underlying **technical problem** to be solved by the present application can be considered to lie in the provision of an alternative recombinant Fel d 1 fusion product.

The **solution** provided by the Applicant to solve the above problem is a recombinant Fel d 1 fusion product comprising a Fel d 1 chain 1, a Fel d 1 chain 2 and a linker selected from a carbon-nitrogen bond or a peptide bond having from 1 to 9 amino acid residues.

Starting from **D1 or D2**, the person skilled in the art would not consider reducing the length of the linker with any expectation of maintaining the immunological properties of the protein. Neither D1 nor D2, nor any of the available prior art, suggests the use of a shorter peptide linker to link chain 1 and chain 2 of Fel d 1 and thereby provide the recombinant Fel d 1 fusion product of the present application.

The use of a shorter peptide, i.e. a carbon-nitrogen bond or a 1-9 amino acids residue in length, significantly reduces the risk of sensitisation to the linker during therapy. The recombinant Fel d 1 fusion protein of the present application mimics the structure and allergenic activity of native Fel d 1.

Therefore, in view of the above, an inventive step can be acknowledged for the subject-matter of the present application.

6. Industrial Applicability (**Article 33(4) PCT**)

6.1. The subject-matter of present **claims 1-18, 20 and 21** is susceptible of industrial applicability as defined in **Article 33 (4) PCT**.

6.2. For the assessment of the present **claim 19** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical

treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

7. The present application does not satisfy the criterion set forth in **Article 6 PCT** because the following claims are not clear.

7.1. The expression "fragment thereof" renders **claims 8 and 9** unclear.
This expression is vague and indefinite because it does not indicate either the length of the fragment, the region of the Fel d 1 chain ½ to which the fragment corresponds, the function of fragment, or any particular characteristic/s that the fragment should have.

7.2. **Claims 8 and 9** lack clarity due to the term "homologue".
Considering that the expression "homology" is used to refer to the degree of similarity between different peptides sequences (see Chambers Dictionary of Science and Technology, page 567) the above term "homologue" is not suitable to clearly define the scope of claims 8 and 9 because its vagueness in not indicating the degree of homology makes it entirely opened to individual interpretation.

7.3. The expression "...substantially..." (**claims 8 and 9**), is not suitable to clearly define the scope of the claims, because it is without technical significance and its vagueness makes it entirely opened to individual interpretation.

7.4. The applicant is informed that expressions like "preferably" and "particularly preferably" (**claims 4 and 10**) have no limiting effect on the scope of the claims, that is to say, the features following any such expressions are to be regarded as entirely optional (see the **Guidelines for Preliminary Examination (PCT) CIII 4.6**).

SECTION VII

8. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents **D1 and D2** is not mentioned in the description, nor are these

documents identified therein.

Claims

1. A recombinant Fel d 1 fusion product comprising a Fel d 1 chain 1, a Fel d 1 chain 2 and a linker selected from a carbon-nitrogen bond or a peptide linker having from 1 to 9 amino acid residues which links the N-terminal amino acid of one chain to the C-terminal amino acid of the other chain.

2. A fusion product as claimed in claim 1, wherein the linker links the N-terminal amino acid of the chain 1 to the C-terminal amino acid of the chain 2.

3. A fusion product as claimed in claim 1 or 2, wherein the linker is a carbon-nitrogen bond.

4. A fusion product as claimed in claim 1 or 2, wherein the short peptide has from 1 to 5 amino acid residues and preferably from 1 to 3 amino acid residues.

5. A fusion product as claimed in any preceding claim, wherein the linker comprises a target site for a reagent capable of selective cleavage of the linker.

6. A fusion product as claimed in claim 5, wherein the reagent is an enzyme.

7. A fusion product as claimed in any preceding claim, wherein the chain 1 and the chain 2 are covalently bonded together by one or more disulfide bridges into an antiparallel arrangement.

8. A fusion product as claimed in any preceding claim, wherein the Fel d 1 chain 1 comprises a sequence of SEQ ID NO 1, or a homologue or fragment thereof which provides substantially the same allergenic properties as SEQ ID NO 1.

9. A fusion product as claimed in any preceding claim, wherein the Fel d 1 chain 2 comprises a sequence of SEQ ID NO 2, SEQ ID NO 3, or a homologue or fragment thereof